REMARKS

The Claim Amendments

Applicants have amended claim 1 to more particularly recite the claimed invention. Specifically, applicants have recited the phrase "wherein each of said fludarabine and said compound 181 are independently present in a therapeutically effective amount" after subsection (a) and (b) and before subsection (c). Support for this amendment is found throughout the specification as filed (e.g., Figure 1 and page 59, paragraph [0066] and at page 53, paragraph [0054]). In case linking claim 1 is found allowable, applicants expressly request rejoinder of withdrawn claim 20 for further examination.

Applicants note that this amendment is made solely to expedite prosecution rather than for any reason related to patentability of the claims.

This amendment adds no new matter. Its entry is requested.

The Rejections

35 U.S.C. § 103(a)

The examiner has maintained the rejection of claim 1 under 35 U.S.C. § 103(a) as being unpatentable over Montgomery (US 4,210,745) (hereinafter "Montgomery") in view of Stamos et al. (WO 00/56331) (hereinafter "Stamos") for the reasons of record. According to the examiner, applicants' anti-cancer data presented in the Jugnu Declaration (filed with the Reply dated May 8, 2009) represent "unexpected results of an 'additive effect' rather than 'a synergistic effect'. The examiner does suggest that a synergistic effect is evident for "the exact individual amount of fludarabine and compound 181" and thereafter suggests what that milligram amount would be (e.g., 5 mg of fludarabine and 6.7 mg of compound 181). Applicants respectfully traverse the rejection to the extent that it is maintained over claim 1 as amended, for the reasons of record and for the following reasons.

As discussed above and solely to expedite prosecution, applicants have amended claim 1 to recite that compound 181 and fludarabine are present in therapeutically effective amounts. Claim 1, as amended, thus provides a novel, synergistic combination of compound 181 and fludarabine that is neither taught nor suggested by Montgomery or Stamos.

Furthermore, although the examiner has suggested that "the synergistic effect is the exact individual amount of (a) fludarabine, and the exact individual amount of (b) compound 181, for example, 5 mg of (a) and 6.7 mg of (b) produces unexpected synergistic effects" such a restriction on the calculated amount of each compound in the combination would unfairly deprive applicants of the full scope of their invention. For instance, applicants demonstrated surprising and unexpected synergistic activity for the claimed combination at particular *in vitro* concentrations in the specification (e.g., Figure 1). More specifically, in ¶ 7 of the Jain Declaration, it was shown that four particular *in vitro* concentrations (e.g., 0.01 μM, 0.1 μM, 1.0 μM and 10.0μM) of the combination of fludarabine and compound 181 induced apoptosis in Daudi cells (a human hematological cancer cell line). Although only these four inhibitor concentrations were tested and represented on the plot in Figure 1, one skilled in the art could conclude that *in vitro* concentrations in the range of from about 0.5μM to about 10μM or greater would produce the strongly synergistic effect when measured as percent apoptosis of the Daudi cells.

Furthermore, since the concentrations tested are representative of an *in vitro* setting, the actual therapeutic amount necessary in an *in vivo* setting will vary according to factors well recognized in the pharmaceutical arts. Thus, one skilled in the art would look to a concentration or dosage range (e.g., from about 0.5μM to 10μM or greater) rather than a fixed amount when deciding on a treatment regimen for a patient (e.g., a regimen that provides a therapeutically effective amount of each compound in the combination). Moreover, applicants have provided general dosage guidance for patients in the specification as filed (e.g., see paragraphs [0054] to [0055] at pages 53-54). As discussed therein, the amount of active ingredients (e.g., fludarabine and compound 181) in a particular dosage "will vary depending on the host treated and the particular mode of administration." In other words, one skilled in the art would calculate a therapeutically effective dose for a particular patient ranging from about 0.5μM (approximately where strong synergy is evident in the Figure 1 plot) each of compound 181 and fludarabine to approximately 10 μM (where strong synergy is most evident) or greater of each compound in the claimed combination. Therefore, applicants respectfully suggest that reciting a dosage with any more particularity in claim 1 (as suggested by the examiner) would unfairly deprive applicants of the full scope of their invention.

Furthermore, the unexpected synergistic effect (as opposed to merely additive) and the enhanced anti-cancer profile possessed by the therapeutically effective amounts of the claimed combination renders it non-obvious over Montgomery in view of Stamos. Accordingly, applicants respectfully request that the examiner withdraw this § 103(a) rejection.

Non-statutory Double Patenting

The examiner has again rejected claim 1 under the judicially created doctrine of obviousness-type double patenting, as being unpatentable over claim 11 of U.S. Patent No. 6,498,178 (hereinafter the "'178 patent"). Applicants respectfully traverse the rejection to the extent that it is maintained over claim 1 as amended, for the reasons of record and for the arguments presented above.

As discussed in the § 103(a) rejection section *supra*, the combination of compound 181 and fludarabine in a therapeutically effective amount recited in claim 1 represents a non-obvious patentable invention over Montgomery and Stamos because it provides an unexpected synergistic effect resulting in an enhanced anti-cancer profile. By analogy, the presently claimed synergistic combination is an unobvious, patentable invention over the '178 patent because the '178 patent provides no teaching, suggestion or motivation to select the claimed combination in a therapeutically effective amount and expect it to have this synergistic anti-cancer effect.

Moreover, the Manual of Patent Examination Procedure (MPEP) states that "[a] double patenting rejection of the obviousness-type>, if not based on an anticipation rationale,< is 'analogous to [failure to meet] the nonobviousness requirement of 35 U.S.C. 103' " (see MPEP § 804 II.B.1 quoting *In re Braithwaite*, 379 F.2d 594, 154 USPQ 29 (CCPA 1967). The MPEP further states that "[t]herefore, *>the< analysis employed in an obviousness-type double patenting rejection parallels the guidelines for analysis of a 35 U.S.C. 103 obviousness determination" (see MPEP § 804 II.B.1 quoting *In re Braat*, 937 F.2d 589, 19 USPQ2d 1289 (Fed. Cir. 1991); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985)). The relevant factual inquiries are as set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966) and include any objective indicia of non-obviousness. Importantly, if these indicia include evidence that the compounds possess superior and unexpected properties then such a showing should be sufficient to rebut a *prima facie* case of obviousness whether related to a § 103 rejection or a nonstatutory obviousness-type double patenting rejection.

Therefore, for all the reasons of record and those presented above, the present application is an unobvious, patentable invention over the '178 patent. Accordingly, applicants respectfully request that the examiner withdraw this nonstatutory obviousness-type double patenting rejection over the '178 patent.

Conclusion

Applicants respectfully request that the examiner consider the foregoing amendments and remarks and allow the pending claims to pass to issue.

Respectfully submitted,

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